



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) Publication number: 0 545 478 A1

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 92203656.1

(51) Int. Cl.⁵: C07D 413/06, A61K 31/33,
C07D 403/06, C07D 263/44

(22) Date of filing: 26.11.92

(30) Priority: 03.12.91 GB 9125726
31.03.92 GB 9207055
30.07.92 GB 9216237

(22) Inventor: Macleod, Angus Murray
24 Abbotts Way, Thorley Park, Bishops
Stortford
Hertfordshire CM23 4YE(GB)

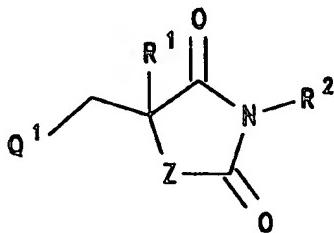
(43) Date of publication of application:
09.06.93 Bulletin 93/23

(74) Representative: Barrett-Major, Julie Diane et
al
Merck & Co., Inc. European Patent
Department Terlings Park Eastwick Road
Harlow Essex CM20 2QR (GB)

>

(54) Heterocyclic compounds as tachykinin antagonists.

(57) Compounds of formula (I):



(I)

EP 0 545 478 A1

wherein

Q¹ represents a phenyl group substituted by one or more halo; naphthyl; indolyl; benzothiophenyl; benzofuranyl; benzyl; or fluorenyl;

R¹ is H, C₁-₆alkyl or C₂-₆alkenyl;

R² is phenyl(C₁-₄alkyl) optionally substituted in the phenyl ring by one or more groups selected from C₁-₆alkyl, C₂-₆alkenyl, C₂-₆alkynyl, halo, cyano, nitro, trifluoromethyl, SR^b, SOR^b, SO₂R^b, OR^b, NR^bR^c, NR^bCOR^c, NR^bCOOR^b or CONR^bR^c, where R^b and R^c independently represent H, C₁-₆alkyl, phenyl or trifluoromethyl; and

Z is O, S, NR^g or CR^gR¹⁰, where R^g represents H, C₁-₆alkyl, phenyl, phenyl(C₁-₄alkyl), COR¹¹, COOR¹¹, CONR^gR¹⁰ where R¹¹ is phenyl, phenyl(C₁-₄alkyl) or C₁-₆alkyl, and R^g and R¹⁰ are each H, C₁-₆alkyl, phenyl or phenyl(C₁-₄alkyl); are tachykinin antagonists. They and their compositions are useful in medicine.

This invention relates to a class of heterocyclic compounds, which are useful as tachykinin receptor antagonists.

The tachykinins are a group of naturally-occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in the peripheral nervous and circulatory systems. The structures of three known mammalian tachykinins are as follows:

5 Substance P:

Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH₂

Neurokinin A:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH₂

10 Neurokinin B:

Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH₂

Substance P is believed *inter alia* to be involved in the neurotransmission of pain sensations [Otsuka et al, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 *Substance P in the Nervous System*, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and 15 Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" TIPS (Dec. 1987) 8 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg et al, *J. Med Chém.* (1982) 25 1009) and in arthritis [Levine et al in *Science* (1984) 226 547-549]. These peptides have also been implicated in 20 gastrointestinal (GI) disorders and diseases of the GI tract such as inflammatory bowel disease [Mantyh et al in *Neuroscience* (1988) 25 (3) 817-37 and D. Regoli in "Trends in Cluster Headache" Ed. Sicuteli et al Elsevier Scientific Publishers, Amsterdam (1987) page 85)]. It is also hypothesised that there is a 25 neurogenic mechanism for arthritis in which substance P may play a role [Kidd et al "A Neurogenic Mechanism for Symmetrical Arthritis" in *The Lancet*, 11 November 1989 and Grönblad et al "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in *J. Rheumatol.* (1988) 15(12) 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as 30 rheumatoid arthritis and osteoarthritis [O'Byrne et al in *Arthritis and Rheumatism* (1990) 33 1023-8]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet et al *Can. J. Pharmacol. Physiol.* (1988) 66 1361-7], immunoregulation [Lotz et al *Science* (1988) 241 1218-21 and Kimball et al, *J. Immunol.* (1988) 141 (10) 3564-9], vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh et al, *PNAS* (1988) 85 3235-9] and, possibly by arresting or slowing β -amyloid-mediated neurodegenerative changes [Yankner et al, *Science* (1990) 250, 279-82], in senile dementia of the Alzheimer type, Alzheimer's disease and Down's Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Luben-Narod et. al., poster to be presented at C.I.N.P. XVIIIth Congress, 28th June-2nd July, 1992, in press], and in disorders of bladder function such as bladder detrusor hyper-reflexia (*Lancet*, 16th May, 1992, 1239).

35 It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders 40 related to immune enhancement or suppression such as systemic lupus erythematosus (European patent application no. 0 436 334), ophthalmic disease such as conjunctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis (European patent application no. 0 394 989).

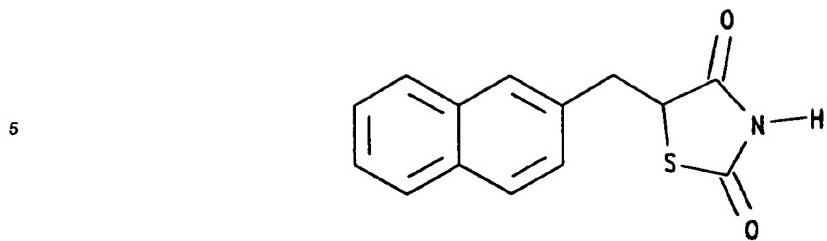
In view of their metabolic instability, peptide derivatives are likely to be of limited utility as therapeutic agents. It is for this reason that non-peptide tachykinin receptor antagonists are sought.

In essence, this invention provides a class of potent non-peptide tachykinin receptor antagonists. By virtue of their non-peptide nature, the compounds of the present invention do not suffer from the shortcomings, in terms of metabolic instability, of the known peptide-based tachykinin receptor antagonists discussed above.

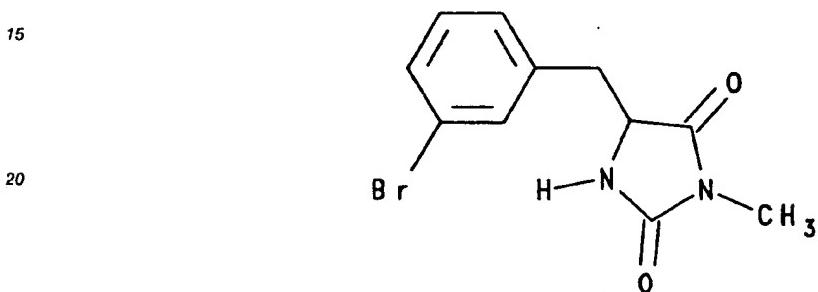
50 J. Indian Chem. Soc., 35, 287-93 (1958) discloses 5-(1-naphthylmethyl)-3-p-tolylhydantoin. No pharmacological activity is attributed to the compound.

Angew. Chem., 95(11), 892-3 (1983) discloses 3-(2-naphthylmethyl)-1-phenylpyrrolidin-2,5-dione. No pharmacological activity is attributed to the compound.

J. Med. Chem., 33(5), 1418-23 (1990) discloses the compound

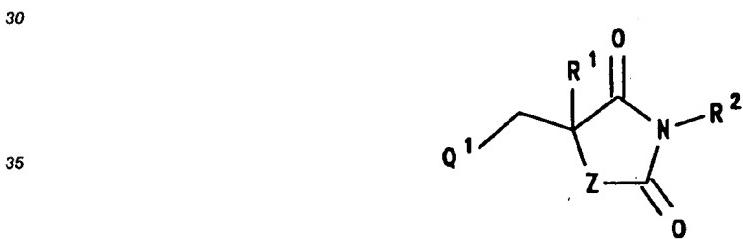


10 which is said to have antihyperglycaemic activity.
J. Med. Chem., 24(4), 465-8 (1981) discloses the compound



25 as having weak anticonvulsant activity.
J. Chem. Soc. (C), 1969, 1855-8 discloses 5-(3-benzo[b]thienyl)-5-methylhydantoin. No pharmacological activity is attributed to the compound.

The present invention provides a compound of formula (I), or a salt or prodrug thereof:



40 (I)

wherein

45 Q¹ represents a phenyl group substituted by one or more halo, optionally substituted naphthyl, optionally substituted indolyl, optionally substituted benzothiophenyl, optionally substituted benzofuranyl, optionally substituted benzyl or optionally substituted fluorenyl;

R¹ represents H, C₁-₆alkyl or C₂-₆alkenyl;

50 R² represents phenyl(C₁-₄alkyl) optionally substituted in the phenyl ring by one or more groups selected from C₁-₆alkyl, C₂-₆alkenyl, C₂-₆alkynyl, halo, cyano, nitro, trifluoromethyl, SR^b, SOR^b, SO₂R^b, OR^b, NR^bR^c, NR^bCOR^c, NR^bCOOR^c, COOR^b or CONR^bR^c, where R^b and R^c independently represent H, C₁-₆alkyl, phenyl or trifluoromethyl; and

55 Z represents O, S, NR⁸ or CR⁹R¹⁰, where R⁸ represents H, C₁-₆alkyl, optionally substituted phenyl, optionally substituted phenyl(C₁-₄alkyl), COR¹¹, COOR¹¹, CONR⁹R¹⁰ where R¹¹ is optionally substituted phenyl, optionally substituted phenyl(C₁-₄alkyl) or C₁-₆alkyl, and R⁹ and R¹⁰ each represents H, C₁-₆alkyl, optionally substituted phenyl or optionally substituted phenyl(C₁-₄alkyl).

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible in vivo into the required compound of formula (I). Conventional procedures for the selection and

preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The compounds according to the invention may exist both as enantiomers and as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The alkyl, alkenyl and alkynyl groups referred to with respect to any of the above formulae may represent straight, branched or cyclic groups, or combinations thereof. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as cyclopropylmethyl; suitable alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

The term "halo" as used herein includes fluoro, chloro, bromo and iodo, especially chloro and fluoro.

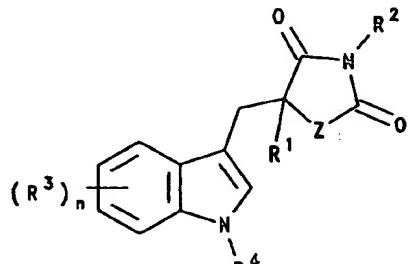
Where R⁸, R⁹, R¹⁰ and/or R¹¹ are optionally substituted phenyl or optionally substituted phenyl-(C₁-₄alkyl), suitable phenyl substituents include C₁-₆alkyl, C₁-₆alkoxy, halo and trifluoromethyl.

Where Q¹ represents optionally substituted fluorenyl, the group is linked through the bridgehead carbon atom, that is to say, C-9.

Where Q¹ represents optionally substituted naphthyl, indolyl, benzothiophenyl, benzofuranyl, benzyl or fluorenyl, suitable substituents include C₁-₆alkyl, C₂-₆alkenyl, C₂-₆alkynyl, halo, cyano, nitro, trifluoromethyl, SR^b, SOR^b, OR^b, NR^bR^c, NR^bCOR^c, NR^bCOOR^c, COOR^b or CONR^bR^c, where R^b and R^c are as above defined. One or more substituents may be present and each may be located at any available ring position, except, where Q¹ is optionally substituted indolyl, the nitrogen atom. Where Q¹ is optionally substituted indolyl, suitable nitrogen substituents include C₁-₆alkyl, optionally substituted phenyl-(C₁-₄alkyl), COOR^b or CONR^bR^c, wherein R^b and R^c are as above defined.

Suitable values of the group Q¹ include 3,4-dichlorophenyl, 3-indolyl, 2-naphthyl, 3-naphthyl, 9-fluorenyl, benzyl, 3-benzothiophenyl and 3-benzofuranyl.

A preferred value of Q¹ is 3-indolyl. For example, compounds of formula (I) having this value of Q¹ include those of formula (Ia), and salts and prodrugs thereof:



(Ia)

wherein R¹, R² and Z are as defined for formula (I);

each R³ may occupy any available carbon atom of the bicyclic ring system and independently represents C₁-₆alkyl, C₂-₆alkenyl, C₂-₆alkynyl, cyano, nitro, halo, trifluoromethyl, SR^b, SOR^b, SO₂R^b, OR^b, NR^bR^c, NR^bCOR^c, COOR^b or CONR^bR^c, where R^b and R^c are as defined for formula (I);

R⁴ represents H, C₁-₆alkyl, optionally substituted phenyl(C₁-₄alkyl), COOR^b or CONR^bR^c, wherein R^b and R^c are as previously defined; and

n is 0, 1, 2 or 3.

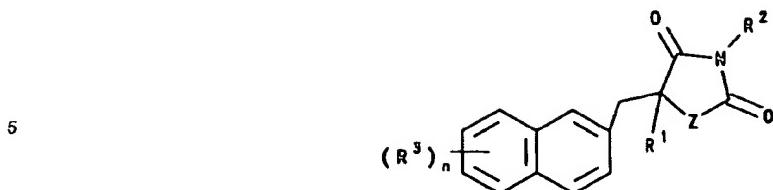
Suitable values for R³ include methyl, methoxy, chloro, fluoro and trifluoromethyl. Preferably R³ represents methoxy.

When R⁴ is optionally substituted phenyl(C₁-₄alkyl), suitable substituents include C₁-₆alkyl, C₁-₆alkoxy, halo and trifluoromethyl.

Suitably R⁴ represents H or C₁-₆alkyl, preferably H or methyl.

Suitably, n is 0.

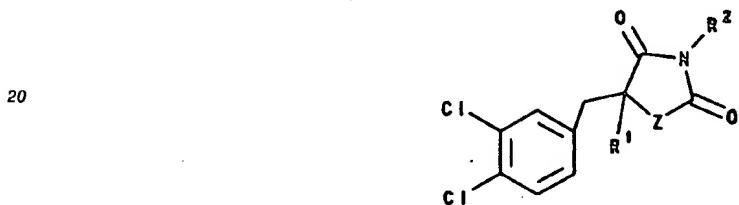
Compounds of formula (I) wherein Q¹ is naphthyl include compounds of formula (Ib), and salts and prodrugs thereof:



10 (Ib)

wherein R¹, R², R³, n and Z are as defined for formula (Ia).

Compounds of formula (I) wherein Q¹ is 3,4-dichlorophenyl are represented by compounds of formula 15 (Ic), and salts and prodrugs thereof:



wherein R¹, R² and Z are as previously defined.

30 A subgroup of compounds of formula (I) is represented by compounds wherein R⁸ represents H, C₁₋₆alkyl, optionally substituted phenyl, optionally substituted phenyl(C₁₋₄alkyl), COR¹¹ or COOR¹¹, where R¹¹ is optionally substituted phenyl or C₁₋₆alkyl.

Within this subgroup may be identified a further subgroup of compounds of formula (I) wherein R¹ represents H or C₁₋₆alkyl.

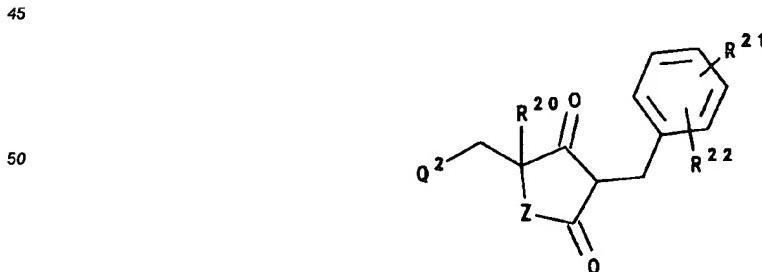
35 With reference to formula (I), preferred values for the group R¹ include H, methyl and 2-propenyl.

Suitably R² represents benzyl. Preferably R² represents substituted benzyl, such as disubstituted benzyl. Preferred substituents include methyl, methoxy, chloro, fluoro, cyano, nitro, phenoxy, amino and trifluoromethyl. More preferably R² represents 3,5-dichlorobenzyl or 3,5-bistrifluoromethylbenzyl.

40 Where Z represents NR⁸, suitable values of R⁸ include H, C₁₋₆ alkyl, such as methyl, phenyl-(C₁₋₄alkyl), such as benzyl, and CONR⁹R¹⁰, such as CONHCH₃ or CONHC₆H₅.

Preferably Z represents O or NR⁸, more preferably O.

A preferred sub-class of compounds according to the invention is represented by compounds of formula (Id), and salts and prodrugs thereof:



wherein Q² is optionally substituted indolyl, optionally substituted naphthyl or halo substituted phenyl;

R²⁰ represents H, C₁-₆alkyl, preferably C₁-₄alkyl, more preferably methyl, or C₂-₆alkenyl, preferably C₂-₄alkenyl, more preferably propenyl;

R²¹ and R²² each independently represent halo or trifluoromethyl; and

5 Z is O, NH, N-phenyl(C₁-₄alkyl), N(C₁-₆alkyl), CONR⁹R¹⁰, where R⁹ and R¹⁰ are as previously defined, or CH₂, more preferably O.

Preferably R²¹ and R²² are located in the 3- and 5-positions of the phenyl ring and are the same, preferably chloro or trifluoromethyl.

Particularly preferred are compounds of formula (Id) wherein Q² is 3-indolyl or N-methyl-3-indolyl, R²⁰ is 10 H or methyl, R²¹ and R²² each represent trifluoromethyl and Z is O.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing 15 a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Thus, for example, when both R¹ and R² are other than 20 hydrogen, the nitrogen atom to which they are attached may be further substituted to give a quaternary ammonium salt. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The invention also provides pharmaceutical compositions comprising one or more compounds of this 25 invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, or suppositories, for oral, parenteral or rectal administration. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tabletting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition 30 may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can 35 be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for 40 administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

45 The compounds of the present invention are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as MS and ALS 50 and other neuropathological disorders such as peripheral neuropathy, for example, diabetic and chemotherapy-induced neuropathy, and posttherapeutic and other neuralgias; respiratory diseases such as chronic obstructive airways disease, bronchopneumonia, bronchospasm and asthma; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis and rheumatoid arthritis;

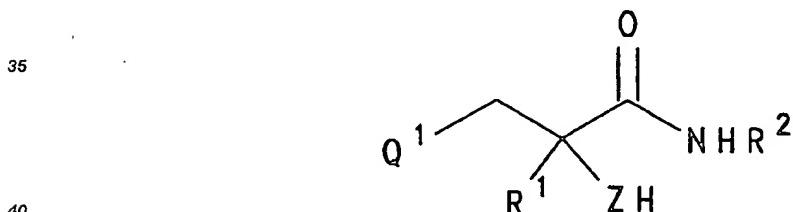
allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of bladder function such as bladder detrusor hyper-reflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

The compounds of formula (I) are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic or peripheral neuropathy and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis and especially migraine.

The present invention further provides a compound of formula (I) for use in therapy. According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of a physiological disorder associated with an excess of tachykinins, especially substance P. The present invention also provides a method for the treatment or prevention of a physiological disorder associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound or composition of this invention.

In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day. For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

According to one process (A) the compounds of the invention wherein Z is O, S or NR⁸ may be prepared from intermediates of formula (III):



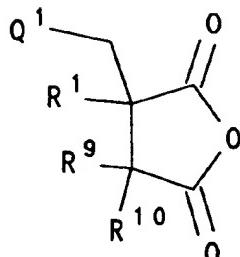
wherein R¹, R² and Q¹ are as defined for formula (I) above and Z is O, S or NR⁸, by reaction with phosgene or a "phosgene equivalent" such as carbonyl diimidazole, a dialkyl carbonate or an alkylchloroformate.

The reaction may be effected under basic conditions. Suitable bases include, for example, metal alkoxides such as sodium methoxide.

The reaction is conveniently effected in a suitable organic solvent such as an ether, for example, tetrahydrofuran, or a halogenated hydrocarbon, for example, dichloromethane, suitably at room temperature.

According to a second process (B) the compounds according to the invention wherein Z is CR⁹R¹⁰ may be prepared from intermediates of formula (IV)

5



10

(IV)

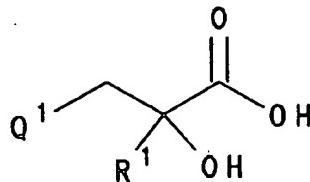
15

wherein R¹, R⁹, R¹⁰ and Q¹ are as defined for formula (I), by reaction with a compound of formula R²NH₂ at elevated temperature.

According to an alternative process (C) compounds of the invention wherein Z is O, may be prepared from intermediates of formula (V):

20

25



30

(V)

wherein R¹ and Q¹ are as defined for formula (I), by reaction with carbonyldiimidazole in the presence of a base, followed by a compound of formula R²NH₂.

35

Suitable bases of use in the reaction include organic bases, such as tertiary amines, for example, triethylamine.

The reaction is conveniently effected in a suitable organic solvent, for example, a halogenated hydrocarbon, for example, dichloromethane, suitably at room temperature.

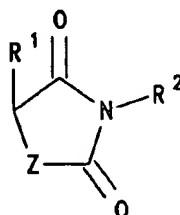
40

The above described process (C) constitutes a novel one-pot synthesis of compounds of formula (I).

According to another general process (D) compounds of formula (I) may be prepared from intermediates of formula (VI)

45

50



(VI)

55

where R¹, R² and Z are as defined for formula (I), by reaction with a reagent suitable to introduce the group Q¹CH₂, such as, for example, a halide of formula Q¹CH₂-Hal, where Hal represent halo such as chloro, bromo or iodo, in the presence of a base.

Suitable bases of use in the reaction include, for example, alkali metal hydrides, such as sodium hydride.

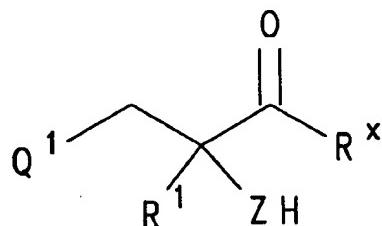
The reaction is conveniently effected in a suitable organic solvent, such as an amide, for example dimethylformamide, or an ether, for example, tetrahydrofuran.

5 Compounds of formula (I) may also be prepared from other compounds of formula (I) or protected derivatives thereof by interconversion processes. Thus, for example, a compound of formula (I) wherein R¹ is C₁-6alkyl may be prepared from the corresponding compound of formula (I) wherein R¹ is H, or a suitably protected derivative thereof, by alkylation, for example, using an alkyl halide.

Intermediates of formula (III) may be prepared from compounds of formula (VII)

10

15



20

(VII)

25 wherein

R¹ and Q¹ are as defined for formula (I), Z is as defined for formula (III), and R^x is an alkoxy, halo, hydroxy or OCOR^y group where R^y is alkyl, by reaction with a compound of formula R²NH₂.

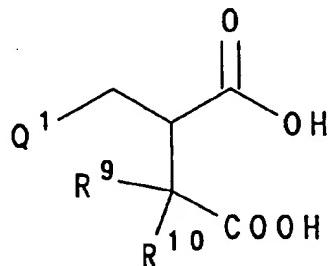
Suitable reaction conditions for the amide bond forming reaction will be readily apparent to those skilled in the art. Where R^x represents hydroxy, the reaction is desirably conducted in the presence of a coupling agent, such as dicyclohexylcarbodiimide.

The group ZH is suitably protected during the course of the amide bond forming reaction.

Compounds of formula (IV) wherein R¹ is H may be prepared from the corresponding compounds of formula (VIII):

35

40



45

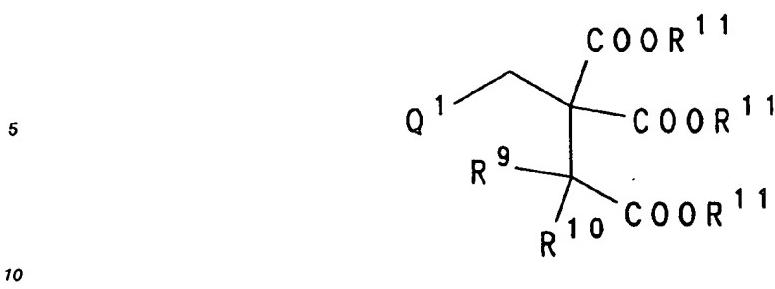
(VIII)

50 wherein R⁹, R¹⁰ and Q¹ are as defined for formula (I), by treatment with an anhydride, such as acetic anhydride.

The reaction is suitably conducted at elevated temperature.

Compounds of formula (VIII) may be prepared from compounds of formula (IXA)

55



(IX)

15

wherein R⁹, R¹⁰, and Q¹ are as defined for formula (I) and R¹¹ is H (IXA), by decarboxylation.

Suitable reaction conditions will be readily apparent to those skilled in the art and include heating in the presence of a suitable transition metal, such as copper, and quinoline.

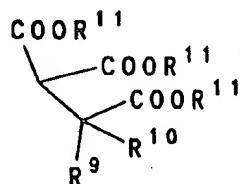
Compounds of formula (IXA) may be prepared from the corresponding compounds of formula (IX) 20 wherein R¹ is alkyl (IXB) by treatment with a suitable base followed by protonation.

Suitable bases include alkali metal hydroxides, for example, sodium hydroxide.

Protonation is suitably effected using an appropriate mineral acid, such as hydrochloric acid.

Compounds of formula (IXB) may be prepared by reaction of compounds of formula Q¹CH₂NR¹²R¹³ 25 wherein R¹² and R¹³ each represent alkyl, with compounds of formula (X):

25



(X)

35

wherein R⁹ and R¹⁰ are as defined for formula (I) and R¹¹ is as defined for formula (IXB), in the presence of catalytic sodium.

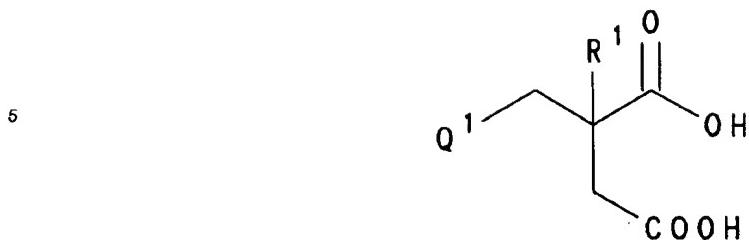
The reaction is conveniently conducted in a suitable organic solvent, such as a hydrocarbon, for 40 example, toluene.

Compounds of formula (X) wherein R⁹ and R¹⁰ are H are commercially available. Compounds of formula (X) wherein R⁹ and R¹⁰ are not both H may be prepared by reaction of a compound of formula CH₂(COOR¹¹)₂ with a compound of formula R⁹R¹⁰C(COOR¹¹)Hal, where Hal represents halo, such as chloro or bromo, in the presence of a base. Suitable bases include, for example, metal hydrides, such as sodium 45 hydride.

Compounds of formula (IV) where R⁹ and R¹⁰ are H may be prepared from intermediates of formula (XI):

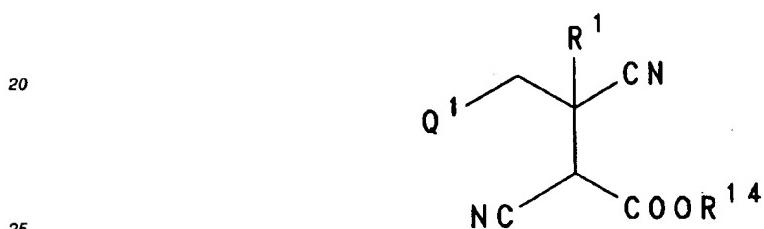
50

55



(XI)

15 wherein R¹ and Q¹ are as defined for formula (I) by treatment with an anhydride, such as acetic anhydride.
Compounds of formula (XI) may be prepared from compounds of formula (XII):



(XII)

30 wherein R¹ and Q¹ are as defined for formula (I) and R¹⁴ is alkyl, by treatment with an acid, such as a mineral acid, e.g. hydrochloric acid, preferably at elevated temperature.
Compounds of formula (XII) may be prepared from compounds of formula (XIII):



(XIII)

by reaction with an alkali metal cyanide, such as sodium cyanide.

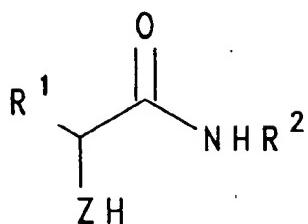
45 The reaction is conveniently effected in a suitable solvent, such as an aqueous alcohol, e.g. aqueous ethanol, preferably at elevated temperature.

Compounds of formula (XIII) may be prepared from compounds of formula Q¹CH₂COR¹ by reaction with a compound of formula NCCH₂CO₂R¹⁴ in the presence of an acid, such as an organic acid, e.g. acetic acid.

The reaction is conveniently effected in a suitable organic solvent, such as a hydrocarbon, e.g. benzene.

50 Compounds of formula (V) are commercially available or may be prepared by known methods or methods analogous thereto.

Intermediates of formula (VI) wherein Z is O, S or NR² may be prepared from compounds of formula (XIV)



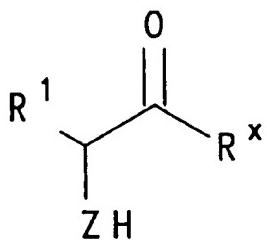
10

(XIV)

wherein R¹ and R² are as defined for formula (I) and Z is O, S or NR³, as described for the preparation of compounds of formula (I) from compounds of formula (III).

15 Compounds of formula (XIV) may be prepared from compounds of formula (XV)

20



25

(XV)

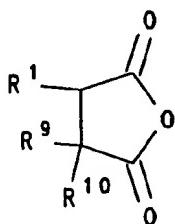
30

wherein R¹, Z and R² are as defined for formula (VII) above, similarly to the preparation of compounds of formula (III) from compounds of formula (VII).

Compounds of formula (XV) are commercially available or may be prepared from commercially available compounds by conventional procedures well-known to those skilled in the art.

35 Intermediates of formula (VI) wherein Z is CR⁹R¹⁰ may be prepared from compounds of formula (XVI)

40



45

(XVI)

50 wherein R¹, R⁹ and R¹⁰ are as defined for formula (I), by reaction with a compound of formula R²NH₂ at elevated temperature.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated, suitably by conventional techniques such as preparative chromatography.

55 The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-

tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wutts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

10 The following non-limiting Examples illustrate the preparation of compounds according to the invention.

EXAMPLE 1: 3-(3,5-Bistrifluoromethylbenzyl)-5-(indol-3-ylmethylene)oxazolidin-2,4-dione

a) Indolelactic acid 3,5-bistrifluoromethylbenzylamide

15 Indolelactic acid (2.0g) suspended in dichloromethane (25ml) was treated with triethylamine (2.8ml) and tert-butyldimethylsilyl triflate (2.3ml) for 16 hours. Triethylamine (2ml) was then added followed by iso-butylchloroformate (1.5ml). After stirring for 30 minutes 3,5-bistrifluoromethylbenzylamine (2.5g) was added and the reaction stirred a further 2 hours. The mixture was washed with 2N hydrochloric acid, aqueous sodium bicarbonate and water, then dried (Na_2SO_4) and concentrated. Chromatography on silica gel, eluting with ethyl acetate-petroleum ether (1:3) gave an oil which was treated with tetrabutylammonium fluoride (20ml of a 1M solution in tetrahydrofuran) for 16 hours. The solution was concentrated, diluted with dichloromethane, washed with water, dried and concentrated. The residue was purified by chromatography (eluting with ethyl acetate-petroleum ether), followed by crystallisation from diethyl ether-petroleum ether to give the title compound as a white crystalline solid, mp 119 °C; found: C, 56.08; H, 3.85; N, 6.43; $\text{C}_{20}\text{H}_{16}\text{F}_6\text{N}_2\text{O}_2$ requires C, 55.82; H, 3.75; N, 6.51.

b) 3-(3,5-Bistrifluoromethylbenzyl)-5-(indol-3-ylmethylene)oxazolidin-2,4-dione

30 A solution of the product of part (a) (230mg) in tetrahydrofuran (1ml) was stirred with carbonyl-diimidazole (160mg) for 1 hour. The reaction mixture was then chromatographed on silica gel eluting with ethyl acetate-petroleum ether (1:3) to give the title compound as a white solid, mp 145-146 °C; found: C, 55.33; H, 3.29; N, 6.09; $\text{C}_{21}\text{H}_{14}\text{F}_6\text{N}_2\text{O}_2$ requires C, 55.27; H, 3.09; N, 6.14.

35 **EXAMPLE 2: 3-(3,5-Bistrifluoromethylbenzyl)-5-(indol-3-ylmethylene)imidazolidin-2,4-dione**

a) L-Tryptophan 3,5-Bistrifluoromethylbenzylamide Hydrochloride

40 To a stirred solution of N-Boc-L-tryptophan (5g) and 1-hydroxybenzotriazole (2.48g) in dimethyl formamide (85ml) was added 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (3.15g) at 0 °C. After 30 minutes 3,5-bistrifluoromethylbenzylamine (4.43g) was added and stirring continued for 16 hours at 25 °C. The reaction mixture was diluted with dichloromethane and washed with sodium bicarbonate solution, water and dried (Na_2SO_4). The solvents were evaporated *in vacuo* to give a white solid which was dissolved in methanolic hydrogen chloride and allowed to stand for 16 hours. Concentration under reduced pressure afforded the title compound as a solid.

b) 3-(3,5-Bistrifluoromethylbenzyl)-5-(indol-3-ylmethylene) imidazolidin-2,4-dione

50 The product of part (a) (10.0g) in dichloromethane (50ml) was treated with triethylamine (5.9ml) and carbonyl diimidazole (3.5g). After stirring for 16 hours the mixture was washed with citric acid solution, then aqueous sodium bicarbonate solution, and dried (MgSO_4). The solvent was evaporated and the residue purified by chromatography on silica gel eluting with ethyl acetate-petroleum ether (bp 60-80 °C), 1:1. The product was recrystallised from diethyl ether-petroleum ether to give the title compound (840mg), mp 151 - 153 °C; found: C, 55.69; H, 3.55; N, 9.25; $\text{C}_{21}\text{H}_{15}\text{F}_6\text{N}_3\text{O}_2$ requires: C, 55.39; H, 3.32; N, 9.23.

EXAMPLE 3: 1-(3,5-Bistrifluoromethylbenzyl)-3-(indol-3-ylmethylene)pyrrolidin-2,5-dionea) 3,3-Dicarboxy-4-(indol-3-yl)butanoic acid

Gramine (17.4g) and triethyl 1,1,2 - ethanetricarboxylate (24.6g) were suspended in dry toluene. Sodium (0.05g) was added and the stirred reaction was heated at reflux for six hours. The reaction mixture was cooled, washed with 2N hydrochloric acid (100ml) and the organic layer was dried ($MgSO_4$) and evaporated. The resulting brown oil was dissolved in ethanol (400ml) and potassium hydroxide (56g) was added. The reaction was heated to reflux for six hours, cooled, poured onto ice and acidified to pH1 with 5N hydrochloric acid. The mixture was saturated with sodium sulphate and extracted with ethyl acetate, dried (Na_2SO_4), filtered and evaporated. The resulting oil was crystallised from 1,2 - dichloroethane (400ml) to yield the title compound, mp 184-185 °C; found: C, 55.33; H, 4.67; N, 4.32; $C_{14}H_{13}NO_6 \cdot 0.75(H_2O)$ requires C, 55.17; H, 4.80; N, 4.60%.

b) 3-Carboxy-4-(indol-3-yl)butanoic acid

3,3-Dicarboxy-4-(indol-3-yl)butanoic acid (10.0g) was dissolved in freshly distilled quinoline (50ml) under dry nitrogen and copper powder (1.0g, 40-80 mesh) was added. The reaction mixture was treated with ultrasound for 0.5 hours and heated to 125 °C for 0.75 hours and 145 °C for 1 hour. The reaction was cooled and poured onto ice, acidified with 5N hydrochloric acid and saturated with sodium sulphate. The mixture was extracted with ethyl acetate (4 x 100ml). The combined organic extract was extracted with 5% sodium bicarbonate solution and the combined aqueous extract was poured onto ice, acidified with 5N hydrochloric acid, saturated with sodium sulphate and extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The resulting oil was taken up into 1,2 dichloroethane and heated and scratched to induce crystallisation. Filtration gave the title compound as white crystals, mp 144-145 °C; found: C, 62.93; H, 5.48; N 5.62; $C_{13}H_{13}NO_4$ requires C, 63.15; H, 5.30; N, 5.67%

c) 3-(indol-3-ylmethylene)succinic anhydride.

The product of part (b) (5.35g) was dissolved in acetic anhydride (100ml) and heated to reflux for six hours. The reaction mixture was cooled and the solvent was removed by evaporation under reduced pressure. The residue was azeotroped with xylene and crystallised from dichloromethane and petroleum ether (bp 60-80 °C) to give the title compound, mp 90-91 °C, found: C, 67.05; H, 4.99, N, 5.95 $C_{13}H_{11}NO_3 \cdot 0.125(H_2O)$ requires C, 67.45; H, 4.90; N, 6.05%.

d) 1-(3,5-Bistrifluoromethylbenzyl)-3-(indol-3-ylmethylene)pyrrolidin-2,5-dione

The product of part (c) (1.5g) and 3,5 bistrifluoromethylbenzylamine (1.9g) were dissolved in xylene (100ml) and heated to reflux under Dean Stark conditions for 16 hours. The reaction mixture was cooled and evaporated and the resulting oil was purified by column chromatography using ethyl acetate-petroleum ether (2:3) on silica gel to yield the title compound as a white solid, mp 68-69 °C; found: C, 58.46; H, 3.77; N, 6.16. $-C_{22}H_{16}F_6N_2O_2$ requires C, 58.16; H, 3.55; N, 6.17%

EXAMPLE 4: a)3-(3,5-Bistrifluoromethylbenzyl)-5-methyl-5-(1-methylindol-3-ylmethylene)oxazolidin-2,4-dione, b) 3-(3,5-bistrifluoromethylbenzyl)-5-methyl-5-(indol-3-ylmethylene)oxazolidin-2,4-dione and c) 3-(3,5-bistrifluoromethylbenzyl)-5-(1-methylindol-3-ylmethylene)oxazolidin-2,4-dione

The product of Example 1 (147mg) in tetrahydrofuran (2ml) under an atmosphere of nitrogen was treated with sodium hydride (13mg of an 60% dispersion in oil) and methyl iodide (25ml). After stirring for 16 hours water was added and extracted with ethyl acetate. The organic solution was dried (Na_2SO_4), concentrated, and the residue purified by chromatography on silica gel eluting with ethyl acetate-petroleum ether (1:3) to give title compound a), mp 113-114 °C; found: C, 56.96; H, 3.72; N, 5.63. $C_{23}H_{18}F_6N_2O_3$ requires C, 57.05; H, 3.75; N, 5.78.

Further elution gave title compound b), mp 158-159 °C; found: C, 56.32; H, 3.59; N, 5.89. $C_{22}H_{16}F_6N_2O_3$ requires C, 56.18; H, 3.43; N, 5.98.

Further elution gave title compound c); 1H NMR ($CDCl_3$, 250 MHz) 3.36 (1H, dd), 3.45 (1H, dd), 3.64 (3H, s), 4.43 (1H, d), 4.50 (1H, d), 5.10 (1H, t), 6.88 (1H, s), 6.95-7.17 (3H, m), 7.48 (1H, d), 7.60 (2H, s), 7.72 (1H, s); m/e 488 ($Cl^+,[M + NH_4^+]$).

EXAMPLE 5: 3-(3,5-Bistrifluoromethylbenzyl)-5-(5-methoxyindol-3-ylmethylene)oxazolidin-2,4-dione

β -[3-(5-Methoxyindolyl)]-DL-lactic acid (M.J. Gortatowski and M.D. Armstrong, J. Org. Chem., 22, 1217, (1957)) (0.85g) in dichloromethane (15ml) with triethylamine (0.52g) was treated with carbonyl diimidazole (0.6g) and stirred at 20 °C for 0.75 hours. 3,5-Bistrifluoromethylbenzylamine (0.91g) was added and the reaction was stirred for a further 0.75 hours before adding carbonyl diimidazole (0.69g) and stirring for 16 hours. The product was purified by column chromatography on silica using ethyl acetate-petroleum ether (1:1) to give the title compound, mp 147-149 °C; found: C, 54.71; H, 3.53; N, 5.77. $C_{22}H_{16}F_6N_2O_4$ requires C, 54.33; H, 3.32; N, 5.76%.

10

EXAMPLE 6: 3-(2-Propenyl)-3-(3,5-bistrifluoromethylbenzyl)-5-(indol-3-ylmethylene)oxazolidin-2,4-dione

To a solution of the title compound of Example 1 (452mg) in dimethylformamide (30ml) under nitrogen at -78 °C was added potassium hexamethyldisilazide (4ml of a 0.5M solution in toluene). After stirring for 5 minutes allyl bromide (0.12ml) was added and the solution stirred for 30 minutes. Water was then added and the mixture extracted (3x) with diethyl ether. The combined extracts were dried, concentrated and the residue purified by chromatography on silica gel (eluent ethyl acetate petroleum ether 1:4) to give the title compound as a crystalline solid, mp 124 °C (diethyl ether-petroleum ether); found: C, 58.18; H, 3.83; N, 5.51. $C_{24}H_{18}F_6N_2O_3$ requires C, 58.07; H, 3.65; N, 5.64

20

EXAMPLE 7: 3-(3,5-Dichlorobenzyl)-5-(indol-3-ylmethylene)oxazolidin-2,4-dione

To a solution of indole lactic acid (0.5g) in CH_2Cl_2 (10ml) and triethylamine (0.68ml) was added carbonyldiimidazole (0.78g). After stirring 1 hour 3,5-dichlorobenzylamine (0.55g) was added and the solution stirred a further 1 hour. The mixture was eluted through a column of silica gel with ethyl acetate-petroleum ether (1:3) to give the title compound as a crystalline solid, mp 157-158 °C (ethyl acetate-petroleum ether); found C, 58.80; H, 3.82; N, 7.14. $C_{19}H_{14}Cl_2N_2O_3$ requires C, 58.63; H, 3.63; N, 7.20.

EXAMPLE 8: (-)-3-(3,5-Bistrifluoromethylbenzyl)-5-(indol-3-ylmethylene)oxazolidin-2,4-dione

30

Potassium glycinate prepared from D-serine by the method of M. Larcheveque and Y. Petit (Bull. Chim. Soc. Fr, (1989), 130) was dissolved in water which was adjusted to pH2 with concentrated hydrochloric acid. The solution was extracted with diethyl ether (5x) and the combined extracts dried and concentrated to give a colourless liquid.

35

To a mixture of this liquid (1.0g) and indole (1.35g) in CCl_4 (25ml) was added tin tetrachloride (2.1ml) with stirring at 0 °C. After 30 minutes the mixture was diluted with ethyl acetate and 2N sodium hydroxide. The organic solution was separated and the aqueous phase extracted (2x) with ethyl acetate. The aqueous solution was adjusted to pH2 with 5N hydrochloric acid and extracted with ethyl acetate which was then dried and evaporated *in vacuo*. The residual crude L-indole lactic acid (170mg) was treated with 3,5-bistrifluoromethylbenzylamine by the method of Example 5 to give the title compound which was obtained as white crystals after chromatography on silica gel (eluent ethyl acetate-petroleum ether 1:3) and crystallisation from diethyl ether-petroleum ether, mp 170 °C, $[\alpha]_D^{20}$ - 58.5 (C = 1, CH_2Cl_2); found: C, 55.22; H, 3.32; N, 5.84. $C_{21}H_{14}F_6N_2O_3$ requires C, 55.27; H, 3.09; N, 6.14.

45

EXAMPLE 9: 5-Methyl-5-(2-naphthylmethyl)-3-(3,5-bistrifluoromethylbenzyl)oxazolidin-2,4-dionea) L-(+)-Lactic Acid 3,5-bistrifluoromethylbenzyl amide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.5g) was added to a solution of L-(+)-lactic acid (1. 17g) and 1-hydroxybenzotriazole (1.99g) in dimethyl formamide (15ml) at 0 °C under a nitrogen atmosphere. After stirring for 30 mins, 3,5-bistrifluoromethylbenzylamine was added and the solution was stirred at room temperature for 16h. The solution was diluted with dichloromethane (150ml) and washed with sodium bicarbonate solution, water and brine. After drying (Na_2SO_4) the solvent was evaporated *in vacuo* to leave a viscous yellow oil.

55

b) 5-Methyl-3-(3,5-Bistrifluoromethylbenzyl)oxazolidin-2,4-dione

A solution of the product of part (a) (2.3g), N-methylmorpholine (1ml) and 1,1-carbonyldiimidazole (1.89g) in dichloromethane (50ml) was stirred at room temperature for 16h under a nitrogen atmosphere.

5 The solvent was removed and the residue chromatographed on silica gel (eluent ethyl acetate-petroleum ether 1:1) to give the title compound as a colourless oil (1.41g).

c) 5-Methyl-5-(2-naphthylmethyl)-3-(3,5-bistrifluoromethylbenzyl)oxazolidin-1,4-dione

10 Sodium hydride (60mg of a 60% dispersion in oil) was added to a solution of 5-methyl-3-(3,5-bistrifluoromethyl benzyl)oxazolidine-2,4-dione (0.5g) in dimethyl formamide (10ml) at room temperature under a nitrogen atmosphere. After stirring for 5 minutes 2-bromomethylnaphthalene (0.33g) in dimethyl formamide (5ml) was added and the solution was stirred for 5 hours. Dichloromethane (150ml) was added and the solution was washed with water. After drying (Na_2SO_4), the solvent was evaporated and the residue chromatographed on silica gel (eluent ethyl acetate-petroleum ether 1:4) to give the title compound after recrystallisation from diethyl ether, mp 95-97 °C; found C, 59.96; H, 3.44; N, 2.94. $\text{C}_{24}\text{H}_{17}\text{F}_6\text{NO}_3$ requires C, 59.88; H, 3.56; N, 2.91.

EXAMPLE 10: 5-Methyl-5-(3,4-dichlorobenzyl)-3-(3,5-bistrifluoromethylbenzyl)oxazolidin-2,4-dione

20 The title compound was prepared by the method of Example 9c) using 3,4-dichlorobenzyl bromide, and crystallised from diethyl ether-petroleum ether, mp 80-82 °C; found C, 48.10; H, 2.54; N, 2.84. $\text{C}_{20}\text{H}_{13}\text{Cl}_2\text{F}_6\text{NO}_3$ requires C, 48.02; H, 2.62; N, 2.80.

EXAMPLE 11: 1-Benzyl-3-(3,5-bistrifluoromethylbenzyl)-5-(indol-3-ylmethylen)eimidazolidine-2,4-dione

30 A solution of the compound of Example 2 (0.5g) in dry tetrahydrofuran (20ml) was cooled to -78 °C and n-butyl lithium (0.72ml of a 1.6M solution in hexanes) was added with stirring. After 15 minutes benzyl bromide (0.14ml) was added. The solution was allowed to warm to room temperature then heated to reflux for 3 hours, cooled and poured into saturated ammonium chloride solution (20ml). This mixture was extracted with ethyl acetate and the organic layers dried (MgSO_4). The residue was purified by chromatography on silica gel eluting with ethyl acetate-petroleum ether (1:3) to give the title compound, mp 154-156 °C; found: C, 61.66; H, 4.05; N, 7.64; $\text{C}_{28}\text{H}_{21}\text{F}_6\text{N}_3\text{O}_2$ requires: C, 61.65; H, 3.88; N, 7.70.

EXAMPLE 12: 1-Methyl-3-(3,5-bistrifluoromethylbenzyl)-5-(indol-3-ylmethylen)eimidazolidine-2,4-dione

35 Prepared by the method of Example 11 using methyl iodide in place of benzyl bromide, mp 145-147 °C; found: C, 56.54; H, 3.83; N, 8.84; $\text{C}_{22}\text{H}_{17}\text{F}_6\text{N}_3\text{O}_2$ requires: C, 56.30; H, 3.65; N, 8.95.

EXAMPLE 13: 1-Phenylcarboxamido-3-(3,5-bistrifluoromethylbenzyl)-5-(indol-3-ylmethylen)eimidazolidine-2,4-dione

40 A solution of the imidazolidinedione from Example 2 (0.5g) in dry dichloromethane (20ml) was cooled to -78 °C and n-butyl lithium (0.72ml of a 1.6M solution in hexanes) was added with stirring. After 15 minutes phenyl isocyanate (0.12ml) was added. The solution was allowed to warm to room temperature and stirred for a further hour. Water (20ml) was added and the organic layer separated, dried (MgSO_4) and the solvents removed in vacuo. The residue was purified by chromatography on silica gel eluting with ethyl acetate-petroleum ether (1:3) and the product recrystallised from diethyl ether/petroleum ether to give the title compound, mp 170-172 °C; found: C, 58.80; H, 3.61; N, 9.72; $\text{C}_{28}\text{H}_{22}\text{F}_6\text{N}_4\text{O}_3$ requires: C, 58.54; H, 3.51; N, 9.75.

EXAMPLE 14: 1-Methylcarboxamido-3-(3,5-bistrifluoromethylbenzyl)-5-(indol-3-ylmethylen)eimidazolidine-2,4-dione

45 Prepared according to the method of Example 13 using methyl isocyanate, mp 173-175 °C; found: C, 54.53; H, 3.70; N, 10.95; $\text{C}_{23}\text{H}_{18}\text{F}_6\text{N}_4\text{O}_3$. 0.25 Et_2O requires: C, 54.29; H, 3.89; N, 10.55.

The following examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 15A Tablets containing 1-25mg of compound

		Amount mg		
		1.0	2.0	25.0
5	Compound of formula (I)	1.0	2.0	25.0
	Microcrystalline cellulose	20.0	20.0	20.0
	Modified food corn starch	20.0	20.0	20.0
10	Lactose	58.5	57.5	34.5
	Magnesium Stearate	0.5	0.5	0.5

EXAMPLE 15B Tablets containing 26-100mg of compound

		Amount mg		
		26.0	50.0	100.0
15	Compound of formula (I)	26.0	50.0	100.0
	Microcrystalline cellulose	80.0	80.0	80.0
20	Modified food corn starch	80.0	80.0	80.0
	Lactose	213.5	189.5	139.5
	Magnesium Stearate	0.5	0.5	0.5

- 25 The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.

EXAMPLE 16 Parenteral injection

		Amount mg	
		1 to 100mg	
35	Compound of formula (I)	1 to 100mg	
	Citric Acid Monohydrate	0.75mg	
	Sodium Phosphate	4.5mg	
	Sodium Chloride	9mg	
40	Water for Injections	to 1ml	

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The compound of formula (I) is dissolved or suspended in the solution and made up to volume.

EXAMPLE 17 Topical formulation

		Amount mg	
		1-10g	
50	Compound of formula (I)	1-10g	
	Emulsifying Wax	30g	
	Liquid paraffin	20g	
	White Soft Paraffin	to 100g	

- 55 The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is added and stirring continued until dispersed. The mixture is then cooled until solid.

SUBSTANCE P ANTAGONISM ASSAYA. Receptor Expression in Monkey Kidney Cell Line (COS)

5 To express the cloned human neurokinin-1-receptor (NK1R) transiently in COS, the cDNA for the
 human NK1R was cloned into the expression vector pCDM9 which was derived from pCDM8
 (INVITROGEN) by inserting the ampicillin resistance gene (nucleotide 1973 to 2964 from BLUESCRIPT
 SK+ (trademark, STRATAGENE, La Jolla, CA, USA)) into the Sac II site. Transfection of 20 µg of the
 plasmid DNA into 10 million COS cells was achieved by electroporation in 800 µl of transfection buffer (135
 10 mM NaCl, 1.2 mM CaCl₂, 1.2 mM MgCl₂, 2.4 mM K₂HPO₄, 0.6 mM KH₂PO₄, 10 mM glucose, 10 mM N-2-
 hydroxyethyl-piperazine-N'-2-ethane sulphonic acid (HEPES) pH 7.4) at 260 V and 950 µF using the IBI
 15 GENEZAPPER (trademark IBI, New Haven, CT, USA). The cells were incubated in 10% fetal calf serum, 2
 mM glutamine, 100U/ml penicillin-streptomycin, and 90% DMEM media (GIBCO, Grand Island, NY, USA) in
 5% CO₂ at 37 °C for three days before the binding assay.

B. Stable Expression in Chinese Hamster Ovarian Cell Line (CHO)

20 To establish a stable cell line expressing cloned human NK1R, the cDNA was subcloned into the vector
 pRcCMV (INVITROGEN). Transfection of 20 µg of the plasmid DNA into CHO cells was achieved by
 electroporation in 800 µl of transfection buffer supplemented with 0.625 mg/ml Herring sperm DNA at 300 V
 25 and 950 µF using the IBI GENEZAPPER (IBI). The transfected cells were incubated in CHO media [10%
 fetal calf serum, 100 U/ml penicillin-streptomycin, 2 mM glutamine, 1/500 hypoxanthine-thymidine (ATCC),
 90% IMDM media (JRH BIOSCIENCES, Lenexa, KS, USA), 0.7 mg/ml G418 (GIBCO)] in 5% CO₂ at 37 °C
 until colonies were visible. Each colony was separated and propagated. The cell clone with the highest
 number of human NK1R was selected.

C. Assay Protocol using COS or CHO

30 The binding assay of human NK1R expressed in either COS or CHO cells is based on the use of ¹²⁵I-
 substance P (¹²⁵I-SP, from DU PONT, Boston, MA) as a radioactively labeled ligand which competes with
 unlabeled substance P or any other ligand for binding to the human NK1R. Monolayer cell cultures of COS
 or CHO were dissociated by the non-enzymatic solution (SPECIALTY MEDIA, Lavellette, NJ) and resuspended
 in appropriate volume of the binding buffer (50 mM Tris pH 7.5, 5 mM MnCl₂, 150 mM NaCl, 0.04
 mg/ml bacitracin, 0.004 mg/ml leupeptin, 0.2 mg/ml BSA, 0.01 mM phosphoramidon) such that 200 µl of the
 35 cell suspension would give rise to about 10,000 cpm of specific ¹²⁵I-SP binding (approximately 50,000 to
 200,000 cells). In the binding assay, 200 µl of cells were added to a tube containing 20 µl of 1.5 to 2.5 nM
 of ¹²⁵I-SP and 20 µl of unlabeled substance P or any other test compound. The tubes were incubated at
 4 °C or at room temperature for 1 hour with gentle shaking. The bound radioactivity was separated from
 40 unbound radioactivity by GF/C filter (BRANDEL, Gaithersburg, MD) which was prewetted with 0.1%
 polyethylenimine. The filter was washed with 3 ml of wash buffer (50 mM Tris pH 7.5, 5 mM MnCl₂, 150
 mM NaCl) three times and its radioactivity was determined by gamma counter.

45 The activation of phospholipase C by NK1R may also be measured in CHO cells expressing the
 human NK1R by determining the accumulation of inositol monophosphate which is a degradation product of
 IP₃. CHO cells are seeded in 12-well plate at 250,000 cells per well. After incubating in CHO media for 4
 days, cells are loaded with 5µCi of ³H-myoinositol in 1 ml of media per well by overnight incubation. The
 extracellular radioactivity is removed by washing with phosphate buffered saline. LiCl is added to the well at
 final concentration of 10 mM with or without the test compound, and incubation is continued at 37 °C for 15
 min. Substance P is added to the well at final concentration of 0.3nM to activate the human NK1R. After 30
 50 min of incubation at 37 °C, the medium is removed and 0.1 N HCl is added. Each well is sonicated at 4 °C
 and extracted with CHCl₃/methanol (1:1). The aqueous phase is applied to a 1 ml Dowex AG 1X8 ion
 exchange column. The column is washed with 0.1 N formic acid followed by 0.025 M ammonium formate-
 0.1 N formic acid. The inositol monophosphate is eluted with 0.2 M ammonium formate-0.1 N formic acid
 and quantitated by beta counter.

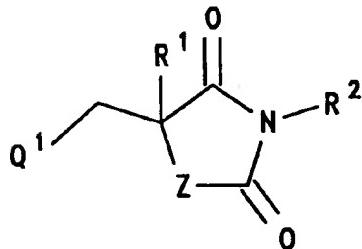
The data in Table 1 were obtained for compounds of formula (I):

TABLE 1

SUBSTANCE P ANTAGONISM RESULTS		
	Compound of Ex #	IC ₅₀ @ NKIR (nM)
5	1	21
10	2	400
15	3	250
20	4a	14
	4b	140
	4c	300
	5	300
	6	50
	7	200
	8	17
	9	>1000
	10	100
	11	630
	12	160
	13	410
	14	85

25 Claims

1. A compound of formula (I)



40 wherein

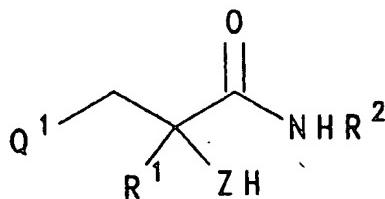
45 R¹ represents a phenyl group substituted by one or more halo, optionally substituted naphthyl, optionally substituted indolyl, optionally substituted benzothiophenyl, optionally substituted benzofuranyl, optionally substituted benzyl or optionally substituted fluorenyl;

R¹ represents H, C₁-₆alkyl or C₂-₆alkenyl;

50 R² represents phenyl(C₁-₄alkyl) optionally substituted in the phenyl ring by one or more groups selected from C₁-₆alkyl, C₂-₆alkenyl, C₂-₆alkynyl, halo, cyano, nitro, trifluoromethyl, SR^b, SOR^b, SO₂R^b, OR^b, NR^bR^c, NR^bCOR^c, NR^bCOOR^c, COOR^b and CONR^bR^c, where R^b and R^c independently represent H, C₁-₆alkyl, phenyl or trifluoromethyl;

55 Z represents O, S, NR^g or CR^gR¹⁰, where R^g represents H, C₁-₆alkyl, optionally substituted phenyl, optionally substituted phenyl(C₁-₄alkyl), COR¹¹, COOR¹¹, CONR⁹R¹⁰ where R¹¹ is optionally substituted phenyl, optionally substituted phenyl(C₁-₄alkyl) or C₁-₆alkyl, and R⁹ and R¹⁰ each represents H, C₁-₆alkyl, optionally substituted phenyl or optionally substituted phenyl(C₁-₄alkyl); or a salt or prodrug thereof.

2. A compound as claimed in claim 1 wherein Q¹ represents a phenyl group substituted by one or more halo, optionally substituted naphthyl or optionally substituted indolyl.
3. A compound as claimed in claim 1 or claim 2 wherein R² represents disubstituted benzyl.
4. A compound as claimed in any preceding claim wherein Z is O.
5. A compound as claimed in claim 1 selected from:
- 3-(3,5-bistrifluoromethylbenzyl)-5-(indol-3-ylmethylene)oxazolidin-2,4-dione;
- 3-(3,5-bistrifluoromethylbenzyl)-5-(indol-3-ylmethylene)imidazolidin-2,4-dione;
- 1-(3,5-bistrifluoromethylbenzyl)-3-(indol-3-ylmethylene)pyrrolidin-2,5-dione;
- 3-(3,5-bistrifluoromethylbenzyl)-5-methyl-5-(1-methylindol-3-ylmethylene)oxazolidin-2,4-dione;
- 3-(3,5-bistrifluoromethylbenzyl)-5-methyl-5-(indol-3-ylmethylene)oxazolidin-2,4-dione;
- 3-(3,5-bistrifluoromethylbenzyl)-5-(1-methylindol-3-ylmethylene)oxazolidin-2,4-dione;
- 3-(3,5-bistrifluoromethylbenzyl)-5-(5-methoxyindol-3-ylmethylene)oxazolidin-2,4-dione;
- 3-(2-propenyl)-3-(3,5-bistrifluoromethylbenzyl)-5-(indol-3-ylmethylene)oxazolidin-2,4-dione;
- 3-(3,5-dichlorobenzyl)-5-(indol-3-ylmethylene)oxazolidin-2,4-dione;
- (-)-3-(3,5-bistrifluoromethylbenzyl)-5-(indol-3-ylmethylene)oxazolidin-2,4-dione;
- 5-methyl-5-(2-naphthylmethyl)-3-(3,5-bistrifluoromethylbenzyl)oxazolidin-2,4-dione;
- 5-methyl-5-(3,4-dichlorobenzyl)-3-(3,5-bistrifluoromethylbenzyl)oxazolidin-2,4-dione;
- 1-benzyl-3-(3,5-bistrifluoromethylbenzyl)-5-(indol-3-ylmethylene)imidazolidine-2,4-dione;
- 1-methyl-3-(3,5-bistrifluoromethylbenzyl)-5-(indol-3-ylmethylene)imidazolidine-2,4-dione;
- 1-phenylcarboxamido-3-(3,5-bistrifluoromethylbenzyl)-5-(indol-3-ylmethylene)imidazolidine-2,4-dione;
- 1-methylcarboxamido-3-(3,5-bistrifluoromethylbenzyl)-5-(indol-3-ylmethylene)imidazolidine-2,4-dione;
- and salts and prodrugs thereof.
6. A compound as claimed in any preceding claim for use in therapy.
7. A process for the preparation of a compound as claimed in claim 1, which process comprises:
- (A) reaction of a compound of formula (III):



40

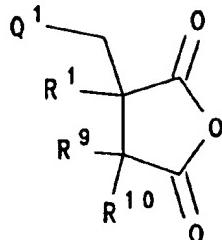
45 wherein R¹, R² and Q¹ are as defined for formula (I) and Z is O, S or NR⁸, where R⁸ is as defined for formula (I), with phosgene or a phosgene equivalent; or

(B) reacting an intermediate of formula (IV)

50

55

5

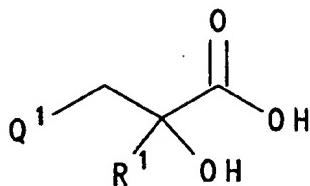


10

(IV)

15 wherein R¹, R⁹, R¹⁰ and Q¹ are as defined for formula (I), with an amine of formula R²NH₂ wherein
R² is as defined for formula (I); or
(C) reacting a compound of formula (V)

20



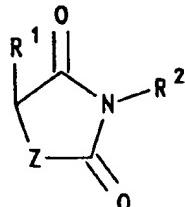
25

(V)

30

wherein R¹ and Q¹ are as defined for formula (I) with carbonyldiimidazole in the presence of a base,
followed by an amine of formula R²NH₂, wherein R² is as defined for formula (I); or
(D) reaction of an intermediate of formula (VI)

35



40

(VI)

- 45 wherein R¹, R² and Z are as defined for formula (I) with a reagent suitable to introduce the group
Q¹CH₂;
- 50 and optionally converting the compound of formula (I) so prepared to another compound of formula (I)
or a salt or prodrug thereof.
- 55 8. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 5 and a
pharmaceutically acceptable carrier therefor.
9. The use of a compound as claimed in any of claims 1 to 5 for the manufacture of a medicament for the
treatment of a physiological disorder associated with an excess of tachykinins.

EP 0 545 478 A1

- 10.** The use of a compound as claimed in any of claims 1 to 5 for the manufacture of a medicament for the treatment of pain or inflammation or disorders associated therewith.

5

10

15

20

25

30

35

40

45

50

55



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 20 3656

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	EP-A-0 313 397 (THE WELLCOME FOUNDATION LTD) * complete document (compounds wherein W is group of formula (i)) * -----	1,8	C07D413/06 A61K31/33 C07D403/06 C07D263/44
X	ARZNEIMITTEL FORSCHUNG. DRUG RESEARCH vol. 9, 1967, AULENDORF DE pages 1145 - 1149 J. GOOTJES ET AL. 'Synthesis and pharmacology of a number of seco analogues of 2-(p-chlorophenyl)-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo(a)quinolizine' * page 1148, compound 21 * -----	1	
A	EP-A-0 343 643 (WARNER-LAMBERT COMPANY) * claims * -----	1,8	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C07D
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	18 JANUARY 1993	VAN BIJLEN H.	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons A : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			